Decision Memo for Nesiritide for Treatment of Heart Failure Patients (CAG-00289N)

Decision Summary

CMS has determined that there is sufficient evidence to conclude that the use of nesiritide for the treatment of chronic heart failure is not reasonable and necessary for Medicare beneficiaries in any setting. This determination applies only to the treatment of chronic heart failure and does not change contractor discretion to cover other off-label uses of nesiritide or use consistent with the current FDA indication for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. Therefore, we will be issuing the following national coverage determination.

Nesiritide for the treatment of chronic heart failure in Medicare beneficiaries will not be covered.

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Decision Memo

TO: Administrative File: CAG #00289N
Nesiritide for Heart Failure Patients

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SUBJECT: Final Decision Memorandum for Nesiritide for Heart Failure Patients
DATE: March 2, 2006

I. Decision

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II. Background

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Cardiac decompensation, which is a manifestation of heart failure, is characterized by signs and symptoms of interstitial volume overload and/or inadequate tissue perfusion. The cardinal manifestations of heart failure are dyspnea (shortness of breath) and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others primarily complain of edema and report few symptoms of dyspnea or fatigue. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term “heart failure” is preferred over the older term “congestive heart failure.” (Harrison’s Principles of Internal Medicine, 16th Edition, 2005).

Epidemiology and Disease Burden

Heart failure is growing in incidence and prevalence within the Medicare population and is associated with rising mortality rates. Though trends primarily reflect the strong association between heart failure and advancing age, they also are influenced by the rising prevalence of precursors such as diabetes, hypertension, and dyslipidemia within industrialized societies and the improved long-term survival of patients with ischemic and other forms of heart disease.

Heart failure affects nearly 5 million Americans, and over 550,000 new cases are diagnosed each year (American Heart Association, 2005). Heart failure is primarily a disease of the elderly. Approximately 78% of men and 85% of women with heart failure are 65 years of age or older; the median age of persons hospitalized with heart failure is 76 years. It accounts for nearly 1 million hospitalizations, causes nearly 50,000 deaths per year (Harrison’s Principles of Internal Medicine 16th Edition, 2005), and is a contributory cause to over 260,000 deaths annually. As the US population ages over the next several decades, it is anticipated that the societal burden of heart failure will continue to rise at a rapid rate (Rich, 2001).

The annual incidence of new cases of heart failure rises from less than 1 per 1000 patient-years younger than age 45, to 10 per 1000 patient-years older than age 65, to 30 per 1000 patient-years older than age 85 (Goldman, 2004). Although the relative incidence and prevalence of heart failure are lower in women than in men, women constitute at least half of the cases because of their longer life expectancy.

Heart failure is the underlying reason for 12 to 15 million office visits and 6.5 million hospital days each year (O'Connell, 2000). During the past 10 years, the annual number of hospitalizations has increased from approximately 550,000 to nearly 900,000 for heart failure as a primary diagnosis, and from 1.7 to 2.6 million for heart failure as a primary or secondary diagnosis (Haldeman, Croft, Giles, Rashidee; 1999). The number of deaths has increased steadily despite advances in treatment.

Despite advances in therapy, the prognosis of patients with heart failure is poor. For those patients that survive the acute onset of heart failure, approximately only 35% of men and 50% of women survive after 5 years. Although it is difficult to predict prognosis, patients with symptoms at rest (class IV) have a 30 to 70% annual mortality rate, patients symptomatic with mild activity (class III) have mortality rates of 10 to 20% annually, and those patients symptomatic only with moderate activity (class II) have a 5 to 10% annual mortality rate. Mortality rates are higher in older patients, men, and patients with reduced ejection fractions and underlying coronary heart disease.

Disease Process

Heart failure may occur as a result of impaired myocardial contractility, increased ventricular stiffness, or impaired myocardial relaxation, a variety of other cardiac abnormalities, or states in which the heart is unable to compensate for increased peripheral blood flow or metabolic requirements. For adults, left ventricular involvement is almost always present even if the manifestations are primarily those of right ventricular dysfunction (fluid retention without dyspnea or rales). Heart failure may result from an acute insult to cardiac function, such as a large myocardial infarction (MI), or, more commonly, from a chronic process. In the United States, ischemic heart disease accounts for three-quarters of all cases. Cardiomyopathies are the second most frequent cause, followed by congenital, valvular, and hypertensive diseases.

Depending on the patient’s course and clinical setting, heart failure can be classified into different groups. These groups are categorized as: systolic or diastolic dysfunction; high output or low output; acute or chronic; right-sided or left-sided; and forward or backward. The main distinction between systolic and diastolic heart failure is the inability of the ventricle to contract normally and expel sufficient blood (systolic dysfunction) or to relax and fill normally (diastolic dysfunction). Systolic dysfunction results in inadequate cardiac output and manifests itself as symptoms related to hypoperfusion. Diastolic dysfunction, which accounts for 20 to 40% of cases of heart failure, is primarily related to resistance to ventricular filling and is generally associated with prolonged ventricular relaxation time. Diastolic heart failure occurs more frequently in women than in men, especially in elderly women. In most patients with heart failure, abnormalities exist in both contraction as well as relaxation of the ventricles. Combined systolic and diastolic abnormalities are common.

Interaction of the Intervention with the Disease Process

Treatment Options

Due to the multiple etiologies and the hemodynamic features of heart failure, there is no simple rule for treatment. The five major components of treatment are: (1) general measures; (2) correction of the underlying cause(s); (3) removal of the precipitating cause(s); (4) prevention of deterioration of cardiac function and; (5) control of the heart failure state. General measures include a moderate dietary sodium restriction, daily weighing (to monitor fluid retention), education about diet and medication compliance, and environmental precautions. Control of the other four components usually involves the use of medication. Chronic heart failure is primarily treated in the outpatient setting.

To control excess fluid, diuretics are commonly used along with diet modification. Medications such as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), aldosterone antagonists, and beta blockers are used to prevent the deterioration of myocardial function. Medications used to enhance myocardial contractility include digitalis, sympathomimetic amines, and phosphodiesterase inhibitors. Other groups of medications commonly used in the treatment of heart failure include vasodilators, anticoagulants, and medications used to manage arrhythmias.

For patients suffering with refractory heart failure (i.e., when the response to ordinary treatment is inadequate), more aggressive management may be required. Before these measures are taken, underlying or precipitating causes that may be amenable to specific surgical or medical treatment should be ruled out. Also, complications from overly vigorous therapy should be addressed. Once these have been excluded, urgent treatment necessitating hospitalization and the use of intravenously-administered vasodilators such as nitroglycerin or phosphodiesterase inhibitors may be required. Patients suffering from refractory heart failure can have an acute exacerbation of the condition. This is known as acute(ly) decompensated heart failure (ADHF).

ADHF is a life-threatening condition for which there are limited treatment options. Patients suffering from advanced ADHF have a 30% risk of mortality within one year (Lee, Rouleau, 2003). On August 10, 2001, the FDA approved nesiritide (Natrecor®) for the intravenous treatment of ADHF patients who have dyspnea at rest or with minimal activities. In this population, the use of nesiritide reduces pulmonary wedge capillary pressure and improves dyspnea. Nesiritide is a human B-type natriuretic peptide derived from E. coli bacteria using recombinant DNA. It has the same 32-amino-acid-sequence as the endogenous peptide, which is produced by the ventricular myocardium. Nesiritide's mechanism of action was demonstrated *in vitro* by relaxing human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the alpha-adrenergic agonist, phenylephrine. Nesiritide is administered as an intravenous bolus, followed by continuous infusion. Because of the potential for hypotension, blood pressure should be monitored closely during nesiritide administration. One of the routes of excretion of nesiritide is through the kidneys.

Recently published medical literature expresses concerns about the safety of nesiritide. Specifically, renal dysfunction (Sackner-Bernstein, Skopicki, Aaronson, 2005) and a trend toward increased mortality (Sackner-Bernstein, Kowalski, Fox, Aaronson, 2005) have been reported. Also of concern is the possible misuse of nesiritide. Though the FDA indication is for the treatment of patients with ADHF, some providers are also using nesiritide intermittently to treat chronic heart failure. The authors express concerns that this off-label use of nesiritide for chronic heart failure poses significant risk to patients.

Because of concerns on nesiritide's safety profile as well as its appropriate use, Scios/Johnson & Johnson (J&J) established an expert panel of cardiologists and heart failure clinicians to review usage and safety data. This expert group, referred to as the "Nesiritide Advisory Panel," first met on June 8, 2005, and considered renal insufficiency, mortality, and the effectiveness of nesiritide. The panel issued a consensus statement, provided advice on the ongoing and planned clinical development program, made recommendations about the appropriate use of the drug, and recommended that Scios immediately conduct an educational campaign. The panel suggested that this campaign should inform physicians about the conditions and circumstances in which nesiritide should and should not be used and should ensure that current and future marketing and sales activities are consistent with the educational program. The Panel's conclusions were sent out as a "Dear Healthcare Provider Letter" on July 13, 2005.

The reports of increased risk of renal disease, increased mortality, and the Nesiritide Advisory Panel recommendations raised concerns at CMS and led to our accepting the external request to review the evidence on the off-label use of nesiritide. An off-label use of a drug is a use that is not included as an indication on the drug's label as approved by the FDA. FDA-approved drugs may be covered under Medicare for off-label use if the contractor determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice. This decision memorandum addresses the off-label use of nesiritide for the treatment of chronic heart failure. It does not address the current FDA indication for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. §1812 (Scope of Part A); § 1832 (Scope of Part B) §1861(s) (Definition of Medical and Other Health Services). Nesiritide is an FDA-approved drug for intravenous use, and is not self-administered. Nesiritide is considered to be within the following benefit categories: inpatient hospital services (§1861 (b)(2)); drugs and biologicals which are not usually self-administered by the patient may be considered to be within the benefit category of "incident to" a physician's service (§1861(s)(2)(A)); and drugs and biologicals which are not usually self-administered by the patient may be considered to be within the benefit category of "incident to" a physician's service rendered to hospital outpatients (§1861(s)(2)(B)).

Medicare does not currently have a National Coverage Determination for nesiritide.

IV. Timeline of Recent Activities

June 29, 2005: CMS opened an NCD to evaluate the use of nesiritide in the Medicare population in response to an external request to determine if nesiritide is reasonable and necessary for the treatment of chronic heart failure in beneficiaries. The initial 30-day public comment period began.

July 29, 2005: End of first public comment period. One hundred thirty-six comments received.

December 2, 2005: CMS posted its Proposed Decision Memorandum for a 30-day public comment period.

January 2, 2006: End of second public comment period. Forty comments received.

V. FDA Status

On August 10, 2001, the FDA approved Natrecor® (nesiritide) with the following labeled indication:

“Natrecor (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of Natrecor reduced pulmonary capillary wedge pressure and improved dyspnea.”

In addition to effects on symptoms, the FDA reviewed hemodynamic variables including pulmonary capillary wedge pressure, right atrial pressure, systolic blood pressure, pulmonary vascular resistance, systemic vascular resistance, and cardiac output. The FDA also studied other variables including renal and cardiovascular status. In assessing renal status, the Vasodilation in the Management of Acute Congestive Heart Failure trial (VMAC) revealed that nesiritide affected the renal status in susceptible individuals, and sometimes resulted in azotemia. When nesiritide was initiated at dosages higher than 0.01 µg/kg/min, there was an increased rate of elevated serum creatinine over baseline compared to standard therapy. In the 30-day follow up period in the VMAC trial, five patients in the nitroglycerin group and nine patients in the nesiritide group required first-time dialysis.

Subsequent label revisions on July 2, 2004, April 20, 2005, and April 29, 2005, reflected changes in dosing instructions and mortality data. On July 13, 2005, Scios and the FDA notified healthcare professionals about the recommendations of the Nesiritide Advisory Panel regarding nesiritide. These recommendations can be found in the section VII.B.7 of this document.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. An improved net health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence we considered during our review. The evidence reviewed to date in this final decision memorandum includes the published medical literature on pertinent clinical trials of nesiritide.

A variety of outcome measures may be appropriate, depending on the setting (acute or chronic). Relief of dyspnea, a subjective judgment, is a short-term outcome measure. Reduction of mortality, hospitalization, development of complications, or the need for other therapies are longer term outcome measures that are more objectively measured.

B. Discussion of Evidence Reviewed

1. Question

Is the quality of evidence adequate to conclude that the use of nesiritide to treat chronic heart failure improves net health outcomes for Medicare beneficiaries?

2. External technology assessments

We did not request an external technology assessment on this issue and are unaware of any assessments that were conducted independently.

3. Internal technology assessments

Literature search methods

Medical literature was identified using MEDLINE, Cochrane Collaborative, and a number of cardiology textbooks. Peer-reviewed articles written in English were reviewed. Search terms included: nesiritide, Natrecor®, heart failure, congestive heart failure, intermittent heart failure, intermittent chronic heart failure, and intermittent congestive heart failure. We identified 12 references pertaining to the intermittent use of nesiritide for chronic heart failure. Three publications were peer-reviewed articles. One article was a case study (Josephson, Barnett 2004), another article was of a non-randomized prospective study (Sheik-Taha 2005), and the final peer-reviewed article was a prospective randomized study (FUSION I, Yancy 2004. There were also numerous abstracts advocating intermittent nesiritide usage (Chung, Menon, Daly et al. 2004; Altschul, Masciello et al. 2003, Altschul, Masciello, et al. 2002; Mulki, Pisano et al. 2003; Squiers, Vora 2003; Bhaskaran, Siegel et al. 2003). There was one literature review article (Silver 2004), and two commentaries (Sackner-Bernstein, Skopicki 2005; Sackner-Bernstein, Kowalski 2005).

Josephson and Barnett followed 35 patients receiving nesiritide infusions in an outpatient heart failure program involving approximately 475 infusions (Josephson, Barnett, 2004). All patients exhibited decompensated heart failure refractory to standard treatment. Baseline characteristics, comorbidities, and risk assessment scores utilizing the prognostic factors in the FUSION I trial were incorporated. Based on risk assessment scores, patients were divided into two groups: a high-risk group (51%) and a low-risk group (49%). Using a follow-up questionnaire, 28 patients (80%) reported improved quality of life and improved symptomatic relief following nesiritide infusion. At twelve weeks post-infusion, 71% of patients in the study were alive and had no hospitalizations (compared to 52% in the FUSION I study). A 29% reduction in hospital stay compared to the year prior with no infusional use of nesiritide (six-and-one-half days compared to nine days) was reported as well. The FUSION I study noted 4.6% mortality in the high-risk group at 12 weeks versus 17.4% mortality in the high-risk standard care patients. A similar mortality rate was noted in the Josephson Barnett study for patients receiving nesiritide at 12 weeks.

The FUSION I study was one of the first large-scale clinical trials to test the safety and feasibility of using serial infusions of nesiritide for heart failure in an outpatient setting (Yancy, Saltzberg, Berkowitz, Berolet, Vijayaraghavan, Burnahm et al. 2004). In this open label (researchers and subjects are aware of the treatment regimen, and are thus susceptible to bias) study, 210 patients suffering from ADHF were assigned to one of three treatment groups: (1) usual care as determined by the investigating physician (n=69); (2) usual care plus 0.005 µg/kg/min of nesiritide given for four to six hours, preceded by a 1.0 µg/kg bolus (n=72); or (3) usual care plus 0.01 µg/kg/min of nesiritide given for four to six hours, preceded by a 2.0 µg/kg bolus (n=69). Primary endpoints included adverse events, serious adverse events (including all-cause death and hospitalization), vital signs, and laboratory assessment. The Minnesota Living with Heart Failure questionnaire was also used. The study treatment period was 12 weeks, with an additional four weeks of follow-up. No statistically significant differences could be found between treatment groups when evaluating deaths or hospitalizations, though patients receiving nesiritide showed trends for more days alive and out of the hospital compared with patients receiving usual care. A prospective analysis defining higher risk subgroups noted a significant decrease in cardiovascular events.

Sheikh-Taha evaluated the benefit of outpatient intermittent nesiritide therapy in chronic heart failure (Sheikh-Taha, 2005). This was a single-center, nonrandomized, open label, prospective study of 14 patients with chronic left ventricular systolic dysfunction undergoing long-term infusion with dobutamine or milrinone at an outpatient cardiac infusion unit. Inclusion criteria included patients who were 18 years of age or older, had refractory symptoms compatible with NYHA class III or IV heart failure, and were intolerant of or refractory to intermittent IV inotropic therapy with dobutamine or milrinone. The patients received “maximum oral therapy with diuretics; ACE inhibitors, angiotensin receptor blockers, or the combination of hydralazine and isosorbide dinitrate; beta blockers; nitrates; and spironolactone.” Patients were excluded if their systolic blood pressure was consistently less than 90 mm Hg or they had biventricular pacemaker placement. At each visit to the cardiac infusion unit, patients received a bolus IV infusion of nesiritide 2µg/kg, followed by 0.01 µg/kg/min given over four to six hours. The patients also received a four-to-six-hour infusion of IV dobutamine 4-6 µg/kg/min or milrinone (loading dose of 50 µg/kg given over 10 min, followed by a maintenance infusion of 0.175-0.375 µg/kg/min). Treatment was administered either once or twice a week, depending on symptoms. Patients were followed for three months after beginning nesiritide therapy. Primary endpoints included changes in NYHA class, hospitalization for worsening heart failure symptoms, frequency of visits to the heart failure center, and any adverse effects due to nesiritide. The results of the study revealed no statistically significant improvement in NYHA classification during the trial. Patients were found to have fewer hospitalizations due to exacerbation of heart failure after starting nesiritide therapy and the difference was statistically significant (p=0.0253). The number of visits to the heart failure clinic for all patients declined on nesiritide therapy; however the difference was not statistically significant (0.0749).

A number of study abstracts evaluating the intermittent use of nesiritide in chronic heart failure were located. Some have been presented at scientific meetings (Chung, Menon, Daly et al. 2004; Altschul, Masciello, Massaro 2003). One of these (Chung et al 2004) was a prospective open-label study with 19 subjects, while another (Altschul et al. 2003) was a retrospective study with 65 subjects. Though both studies showed clinical improvement, both also had significant methodological flaws. Other abstracts are also available (Altschul, Masciello, Massaro 2002; Mulki, Pisano, Colleen, et al. 2003; Squiers Vora, 2003; Golden, Fallick, Barnett 2002; Bhaskaran, Siegel, Barker, et al. 2003). For these studies, subject size ranged between 14 and 30 patients. Case studies, open-label trials, or retrospective reviews were the research designs employed. These abstracts report clinical benefits to patients, but as noted above, they also are plagued with significant methodological shortcomings. When full articles based on these abstracts are published, they may be assessed further.

Sackner-Bernstein et al. also noted increased risk of worsening renal function in patients treated with nesiritide for ADHF (Sackner-Bernstein, Skopicki, Aaronson, 2005). Using electronic and manual searches, as well as clinical trial data obtained by the study authors from the FDA, the authors located five randomized clinical trials and performed a meta-analysis that compared nesiritide with either placebo or active control for ADHF (n=1269). The study revealed that using the FDA-approved doses of nesiritide significantly increased the risk of worsening renal function compared to non-inotrope-based control (RR 1.52, p=0.003), or any control therapy, including non-inotrope and inotrope-based therapy (RR 1.54, p=0.001). Even low-dose nesiritide significantly increased risk compared to non-inotrope and inotrope-based controls (p=0.012 and p=0.006 respectively). This study did note that there was no difference in the need for dialysis between therapeutic groups. Potential limitations of the meta-analysis include variability in control or treatment interventions, variability in management, as well as potential differences in baseline states of available patients despite identical selection criteria.

Nesiritide was also noted to cause hypotension. In Sackner-Bernstein's review of the VMAC trial, patients given the recommended bolus dose (2 µg/kg), followed by a 0.01 µg/kg/min infusion, had an incidence of symptomatic hypotension in the first 24 hours that was similar to patients who received nitroglycerin. When hypotension occurred the duration of symptomatic hypotension was longer with nesiritide than with nitroglycerin. Also, in earlier trials when nesiritide was initiated at doses higher than 2 µg/kg, followed by a 0.01 µg/kg/min infusion, there were more hypotensive episodes. Furthermore, these episodes were of greater intensity, duration, more likely to be symptomatic, and also more likely to require medical interventions.

Sackner-Bernstein and colleagues, using primary reports of completed clinical trials obtained from the FDA and other sources, obtained 12 randomized double -blind controlled trials and performed a pooled analysis evaluating the use of nesiritide in patients with ADHF (Sackner-Bernstein, Kowalski, Fox, Aaronson, 2005). Thirty-day survival was assessed by meta-analysis and Kaplan Meier analysis was used to determine risk of death. After excluding trials which did not meet criteria for the study, three trials remained (Nesiritide Study Group Efficacy Trial (NSGET), Vasodilation in the Management of Acute Congestive Heart Failure (VMAC), and Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor). In this analysis of these 3 trials, 485 patients were randomized to nesiritide and 377 were randomized to control therapy. The results of this study, which used a pooled analysis, revealed that deaths within 30 days tended to occur more often among the patient randomized to nesiritide therapy than to the randomized control group (RR 1.74, CI 0.97-3.12; p=0.059). No specific reason was given for this increased mortality in the nesiritide group. As with other meta-analysis, potential limitations include differing inclusion/exclusion criteria, possible differing treatment protocols, as well as the possibility of heterogeneity.

After the publication of the proposed decision memorandum, we were directed by Scios to an additional study that had been published after our initial evidence review. Peacock and associates performed a multi-center, randomized, double-blind, placebo-controlled pilot study to evaluate the safety and efficacy of a standard care treatment regimen with the addition of either nesiritide or placebo in 237 emergency department/observation unit (ED/OU) patients with decompensated heart failure (Peacock, Holland, Gyarmathy, et al. 2005). This study did not test the management of chronic heart failure subjects with intermittent use of nesiritide in the non-hospital setting. Objective outcome measures included initial admission, length of stay, and inpatient re-hospitalization through 30 days. Two subjective self-assessment outcome measures were used to evaluate change in dyspnea during the study; a visual analogue scale (VAS) and a 7-point ordinal scale. Dyspnea was assessed during the first 12 hours, and also at drug discontinuation. Specific inclusion/exclusion criteria were noted, intent to treat analysis was followed, and safety measures were also defined. Baseline demographics failed to reveal any differences between the two groups, though the use of digoxin was higher in the control group than in the treatment group (48% vs. 34%).

The study revealed that the chance of asymptomatic hypotension was higher in the treatment group than in the control group (10% vs. 3%). It also revealed that nesiritide-treated subjects were more likely than placebo-treated subjects to be terminated due to adverse events (12% vs. 4%). By study day 30, six (3%) subjects were reported to have died; five (4%) were originally reported in the treatment group and one (1%) in the control group (p=0.213 [Fisher's Exact test]). Nesiritide-treated subjects had an 11% reduction in hospitalization from the ED during the index period compared to control subjects (55% control, 49% nesiritide, p=0.436), and fewer nesiritide-treated subjects (30%) were hospitalized from the ED with heart failure than from the control group (38%, p=0.220). Median initial hospital length of stay was similar between the two groups, but after discharge from the index visit, fewer nesiritide-treated subjects (19%) were admitted to the hospital compared to the control group (24% p=0.43 [Fisher's Exact test]. Among patients hospitalized during the index visit, 10% of nesiritide-treated subjects were re-hospitalized through study day 30 compared to 23% of the control patients (p=0.058). Ordinal scale dyspnea scores were similar between treatment groups through the 12-hour collection period, as well as at drug discontinuation. Mean dyspnea scores at baseline on the VAS were the same for the two treatment groups (38.2 for the nesiritide group and 42.0 for the control group).

Several months after the publication of this study, Scios announced that two additional subjects in the nesiritide treatment group had died, and that these deaths had not been appropriately counted in the original report. This raises the number of deaths in the nesiritide-treated group to seven, compared to only one in the control group.

4. MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

There are a number of guidelines available which encourage the use of nesiritide for ADHF (Task Force on Acute Heart Failure of the European Society of Cardiology; Institute for Clinical Systems Improvement 2004; ACC/AHA Guidelines 2005; University of Kentucky Nesiritide BNP Protocol). Most of these guidelines do not mention the intermittent use of nesiritide for chronic heart failure specifically, though they do note the role of nesiritide in patients with ADHF. ACC/AHA recently revealed its 2005 guidelines for heart failure. These guidelines note that nesiritide improves symptoms of acute heart failure, but the guidelines do not recommend the outpatient intermittent or continuous use of nesiritide for heart failure. Rather, the guidelines recommend more definitive studies in this setting as an adjunctive therapy.

CMS contacted a number of national organizations that develop guidelines to see if they had published guidelines for nesiritide usage in chronic heart failure. We were told that they do not currently have guidelines.

6. Professional Society Position Statements

We have not found nor received professional society position statements on this topic.

7. Expert Opinion

In 2005 Scios, the manufacturer of Natrecor® (nesiritide), convened the Nesiritide Advisory Panel to review and assess important data associated with acute heart failure and Natrecor®. In addition, the panel was tasked with providing guidance and counsel on the ongoing and planned clinical development program for the product as well as recommendations for use. The panel reviewed information submitted by Scios which included the original and current package inserts (dated August 2001 and April 2005, respectively), communications that Scios sent to physicians, recent papers by Sackner-Bernstein et al., and other nesiritide publications. After reviewing the data, on June 13, 2005 the panel released a report making recommendations to Scios. The panel's recommendations are the following:

1. The use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated congestive heart failure who have dyspnea at rest, as were the patients in the largest trial that led to approval of the drug (VMAC). Physicians considering the use of nesiritide should consider its efficacy in reducing dyspnea, the possible risk of the drug summarized above, and the availability of an alternative therapy to relieve the symptoms of congestive heart failure.
2. Nesiritide should not be used to replace diuretics. Furthermore, because sufficient evidence is not currently available to demonstrate benefit for the applications listed below, nesiritide should not be used:
    - For intermittent outpatient infusion
    - For scheduled repetitive use
    - To improve renal function
    - To enhance diuresis.
3. Scios should immediately undertake a pro-active educational program to inform physicians regarding the conditions and circumstances in which nesiritide should and should not be used, as described above. Sponsor-supported communications, including review articles of nesiritide, should reflect the above recommendations. Scios should ensure that current and future marketing and sales activities related to nesiritide are consistent with this educational program. (Scios, Inc. 2005)

8. Public Comments

CMS received 136 comments during the initial public comment period, which were discussed in our proposed decision memorandum. Those comments are available for review at http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=163#0629200507292005

CMS received a total of 40 comments during the 30-day public comment period following publication of the proposed decision memorandum. Fifteen comments (38%) were from physicians; eight (20%) were from nurses, nurse practitioners, or clinical nurse specialists providing care at outpatient nesiritide clinics; six (15%) were from pharmacists; and four (11%) were from patients, family members, or acquaintances of patients receiving outpatient nesiritide. Three comments (8%) were from other health professionals who did not specify their professional backgrounds. Three additional commenters (8%) did not state their backgrounds. One comment represented the joint views of the American College of Cardiology and the American Heart Association.

Eighteen of the 40 commenters (45%) supported our decision to restrict coverage of nesiritide to acute(ly) decompensated heart failure. Twenty-one commenters (51%) supported coverage of nesiritide in the outpatient setting and opposed our decision. One commenter (3%) did not express an opinion on coverage of nesiritide.

Commenting physicians were divided on the issue, with seven (47%) in favor of our decision and eight opposed. Seven of the eight (88%) nurses opposed our decision and all eight pharmacists supported our decision. All four commenting patients, family members, or acquaintances of patients receiving outpatient nesiritide opposed our decision and believed that nesiritide should be allowed for intermittent use in patients with chronic heart failure.

A. Comments about the evidence

Further studies are needed
Seven commenters indicated that further studies should be done in the outpatient setting, including FUSION II. They remarked that coverage decisions should not be made by CMS before the results of these studies are available. One of these comments was submitted jointly by the American College of Cardiology and the American Heart Association who stated: “Based on a review of the evidence, the ACC Heart Failure and Transplant Committee and AHA Heart Failure and Transplantation Committee believe that intermittent infusions of nesiritide for the treatment of chronic heart failure on an outpatient basis should occur only in patients who are enrolled in a randomized trial of the use of nesiritide in this patient population (e.g., FUSION II). The risk/benefit ratio of nesiritide used for this clinical indication has not been defined, and only will be defined after the clinical studies are completed. The Committee supports the use of randomized, controlled trials which in the past have provided the needed information on safety and effectiveness in the process of drug approval. Nesiritide should be treated no differently.”

Response: We agree that further studies will help to address the serious concerns about the use of nesiritide. CMS’ decision is based on currently available peer-reviewed medical literature. There were few studies evaluating the intermittent use of nesiritide for patients with chronic heart failure. Most of these studies were limited to abstracts, which, as brief summaries, provide very few details about the specifics of the study design, methods, or results. CMS is aware of the FUSION II study, and is awaiting its results. We note from the published Peacock study and Scios’ subsequent announcement of additional unreported deaths that the nesiritide-treated group had an approximate seven-fold higher death rate compared to the control group in subjects who were studied in a non-inpatient setting.

We look forward to reviewing additional published information when it becomes available.

Limitations of meta-analysis
Two individuals commented on the limitations of the Sackner-Bernstein meta-analysis.

Response: As noted by the commenters, there were certain limitations in the meta-analysis. We reconsidered our review of the evidence section in the proposed decision memorandum and addressed these limitations in the final decision memorandum.

B. Comments on other aspects of the Proposed Decision Memorandum

Hospice patients
One commenter indicated that patients with end-stage heart failure who are eligible for hospice care should be allowed to receive nesiritide in the inpatient hospice environment.

Response: Coverage determinations with respect to hospice care are outside the scope of this NCD review. Payment for expenses incurred for items or services provided in the hospice environment are made subject to § 1862(a)(1)(C), and are based on a determination of whether such items or services are reasonable and necessary for the palliation or management of terminal illness.

Treatment guidelines/Eligibility criteria
Five commenters supported the use of outpatient, intermittent nesiritide in patients who meet certain treatment guidelines and eligibility criteria.

Response: Treatment guidelines are usually established by specialty medical societies. As indicated in section B.5 of this document, "Evidence-based guidelines," these societies have not provided guidelines on the outpatient, intermittent use of nesiritide. Should societies develop them, we would be happy to review evidence-based treatment guidelines and eligibility criteria.

Appropriate reimbursement of healthcare providers

One commenter suggested that Medicare should consider ways to appropriately reimburse healthcare providers for providing appropriate care to heart failure patients (i.e. more frequent office visits, more frequent labs, and home monitoring by physicians and nurse practitioners).

Response: A national coverage determination does not include a determination with respect to the amount of payment for an item or service. (§ 1869(f)(1)(B))

Chronic Decompensated Heart Failure
One commenter suggested the creation of a subcategory called “chronic decompensated heart failure” and further indicated that patients in this subcategory should be eligible to receive nesiritide on an outpatient, intermittent basis.

Response: At this time the medical community does not recognize “chronic decompensated heart failure” as a distinct medical condition.

FDA’s approval of nesiritide
Three commenters questioned FDA’s approval of the drug in any setting due to its untoward side effects.

Response: Comments regarding FDA’s approval process are beyond the scope of a national coverage determination. Comments and concerns regarding FDA’s approval of nesiritide are best directed to FDA.

Political Motivations
Three commenters were concerned that CMS’ decision regarding nesiritide was the result of political pressure.

Response: In assessing whether or not an intervention is reasonable and necessary, CMS reviews the relevant peer-reviewed medical literature for making its coverage decisions. This process is objective and robust, and relies on the principles of evidence-based medicine in making that determination. The NCD is supported by a record and can be challenged pursuant to the procedures established by statute. (§1869(f))

Personal experiences
Fifteen physicians and nurses provided anecdotal reports of their experiences utilizing outpatient, intermittent nesiritide in the treatment of heart failure patients. Four commenters provided testimonials about their personal experiences as patients or about the experiences of a family member or acquaintance who received nesiritide on an outpatient, intermittent basis.

Response: As we noted in the proposed decision memorandum, individual anecdotal reports are not as persuasive as more methodologically rigorous data. While anecdotal comments from the public are informative, they are given less weight than comments that are accompanied by robust clinical evidence.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Nesiritide is an FDA-approved drug for intravenous use, and is not self-administered. Nesiritide is considered to be within the following benefit categories: inpatient hospital services (§1861 (b)(2)); drugs and biologicals which are not usually self-administered by the patient may be considered to be within the benefit category of “incident to” a physician’s service (§1861(s)(2)(A)); and drugs and biologicals which are not usually self-administered by the patient may be considered to be within the benefit category of “incident to” a physician’s service rendered to hospital outpatients (§1861(s)(2)(B)). Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member,” according to §1862(a)(1)(A) of the Social Security Act.

Question

Is the quality of evidence adequate to conclude that the use of nesiritide to treat chronic heart failure improves net health outcomes for Medicare beneficiaries?

Safety Concerns about the Off-Label Use of Nesiritide in the Treatment of Chronic Heart Failure

As summarized in the Evidence Table (Appendix A) and discussed above, the results of some of the articles we reviewed suggest that nesiritide therapy for chronic heart failure may reduce days of hospitalization and improve symptoms. However, this is not a consistent finding across all studies. For example, there was no reported change in NYHA class. Published reports have pointed out safety concerns about nesiritide use in a number of settings. Nesiritide use was associated with worsened renal function and increased mortality. As previously noted in the most recent information submitted by Scios, the Peacock study revealed an approximate seven-fold increase in mortality in patients receiving nesiritide compared to the control group.

Much of the reported research on the use of nesiritide for the intermittent treatment of chronic heart failure appears in abstracts and has not yet been published as full peer-reviewed journal articles. In general, abstracts do not provide sufficient information for us to evaluate the strength of the reported findings critically. As such, these abstracts do not constitute strong evidence and are given less weight than other evidence. The published articles supporting the off-label use of nesiritide for chronic heart failure are hampered by methodological shortcomings, including small sample size and the lack of long term outcome data.

Josephson, Barnett, 2004: This study has a number of limitations, including small sample size (n=35). Though patients were followed for two years, only 12-week mortality was reported, and only the one-year hospitalization rate was reported. Inclusion criteria were not provided, and no reporting of results based on high-risk versus low-risk status was included in the study.

Yancy, Saltzberg, Berkowitz, Berolet, Vijayaraghavan, Burnahm et al. 2004: We note that this study has some methodological limitations, including short duration, open-label design, the use of ill defined usual care, and employment of a prospective analysis to define sub-groups (see Appendix A). Because of the limitations noted in this study, a second study (FUSION II) was initiated in 2004 (Yancy 2004). FUSION II, a double-blind, placebo-controlled trial, will use mortality/cardiorenal hospitalization as a composite end point. This study will randomly assign approximately 900 patients to either treatment with usual care plus nesiritide or usual care plus placebo. We will review those results when they become available.

Sheikh-Taha, 2005: No detailed information was provided about the tolerability of the drug, though course of treatment for two patients was altered due to hypotension secondary to nesiritide. This study is limited by its small sample size (n=14), open label design, lack of randomization, and lack of control group.

Sackner-Bernstein, Skopicki, Aaronson, 2005: A number of limitations were noted in this study, including the unavailability of primary data, the use of a single definition of worsening renal function, the inability to identify and adjust for baseline differences in the treatment groups, and limited information on events or interventions that occurred after the treatment period.

Peacock, Holland, Gyarmathy, et al. 2005: A number of limitations were noted in the study. First, though p-values were reported in the studies, confidence intervals were not included. Also, the study noted that using Fisher's Exact test statistical method, the comparable death rate between the two groups was not statistically significant (p=0.213). But if measures of association are used, (Relative Risk), the nesiritide group had almost a five-fold increase in death compared to the control group (RR=4.74). Though VAS is a validated test for dyspnea measurement, specific information on the 7-point ordinal score measure was not provided, and this raises questions regarding its validity in this setting. It would have been helpful to see confirmation of whether the 7-point ordinal score had been validated against the VAS dyspnea scale. Use of the Dyspnea Fatigue Index score as a validated test to measure dyspnea, or the Kansas City Cardiomyopathy Questionnaire to measure quality of life measures, functional status, or clinical summary would have helped to address these shortcomings. Other limitations noted in the study by the authors include the lack of prospectively defined primary endpoints, a high number of subjects were in NYHA class I or II or had no prior history of heart failure enrollment, and the observation unit environment may confound length of stay data. As noted earlier, this study included patients with decompensated heart failure. This study did not test the management of chronic heart failure subjects with intermittent use of nesiritide in the non-hospital setting.

Considering these weaknesses, along with the incidence of renal dysfunction, the increased incidence of mortality, and the findings and recommendations of the Nesiritide Advisory Panel, we find substantial concerns about the net health outcomes associated with the use of this drug for chronic heart failure. Based on our analysis of the available evidence to date, CMS will be issuing a national non-coverage decision for the use of nesiritide for the treatment of chronic heart failure.

CMS has had discussions with Scios about clinical trials. We believe that further trials of nesiritide can add to the evidence available to support treatment decisions, and we encourage these activities generally as we believe they benefit the public.

IX. Conclusion

CMS has determined that there is sufficient evidence to conclude that the use of nesiritide for the treatment of chronic heart failure is not reasonable and necessary for Medicare beneficiaries in any setting. This determination applies only to the treatment of chronic heart failure and does not change contractor discretion to cover other off-label uses of nesiritide or use consistent with the current FDA indication for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. Therefore, we will be issuing the following national coverage determination.

Nesiritide for the treatment of chronic heart failure in Medicare beneficiaries will not be covered.

Appendices [PDF, 160KB]

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